Synthesis of 1*H*- and 5*H*-1,3-diazepines from azido- and tetrazolo-pyridines

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Stable 1*H*-1,3-diazepines 7–9, 10, 13, 14, 17 and 19 are obtained, often in high yields, by photolysis of trifluoromethyl-substituted azido- or tetrazolo-pyridines in the presence of alcohols or amines; in some cases, 5*H*-1,3-diazepines are also formed (11, 21 and 23).

While 1,4-diazepines have been investigated extensively,[1] the 1,3-diazepines are comparatively little known.[1,2] Herein we report the first syntheses of stable, monocyclic *N*-unsubstituted 1*H*-1,3-diazepines, often in high yields. The compounds carrying CF_3 groups are of special interest in view of their physical and chemical properties.[3]

We have shown previously that 1,3-diazacyclohepta-1,2,4,6-tetraenes **4** are formed very efficiently on matrix photolysis of tetrazoles **1** and/or azides **2** *via* the 2-pyridylnitrenes **3**.[4] The trifluoromethyl groups appear to accelerate the tetrazole–azide tautomerism (**1** ⇄ **2**) and increase the nitrene reactivity,[4] thereby facilitating the formation of **4**. We now report the synthesis of 1,3-diazepines by trapping of **4** with nucleophiles.

Photolysis† of azide **5** in dioxane–methanol (3 : 1) for 80 min at room temperature gave the 2-methoxy-4-trifluoromethyl-1,3-diazepine **7** in 92% yield after Kugelrohr distillation. The same compound was obtained in 47% yield by analogous photolysis of the isomeric tetrazolopyridine **6**. Evidence for the 1*H* structure of **7** is given by the ^1H and ^{13}C NMR spectra.‡ The broad NH signal at δ 4.80 vanished on addition of D_2O. The proton and ^{13}C NMR assignments of this and the following compounds are based on the observed proton and fluorine coupling constants, homonuclear decouplings, DEPT and COSY experiments and Eu(fod)$_3$-induced chemical shifts.[5]

Proof of the diazepine ring structure was obtained by X-ray crystallography of the benzoylation product **8**,‡ obtained in 87% yield (Scheme 1 and Fig. 1). The ring has a pronounced boat structure. This compound was hydrogenated to **9** in 87% yield.‡

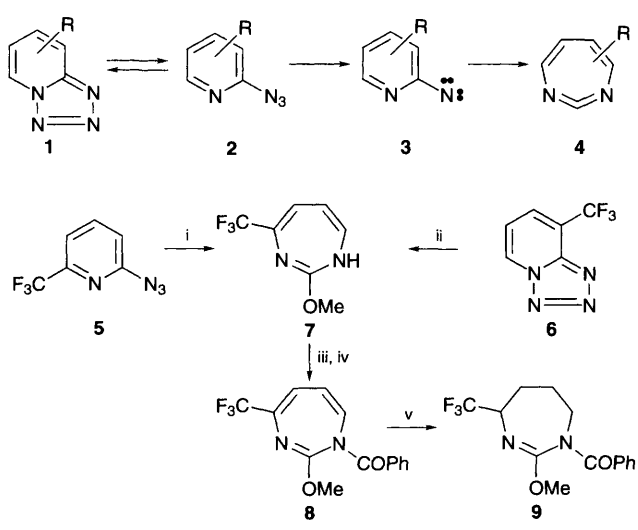
Similar photolysis of **5** in diisopropylamine (DIPA)–dioxane (1 : 3) (Scheme 2) afforded the 1*H*-1,3-diazepine **10** (76%) which, however, isomerised to the 5*H* tautomer **11** on distillation (100 °C) or preparative GC (130 °C).‡

In compounds **7** and **10** the NH proton is specifically located at the 1-position shown as established by ^1H and ^{13}C NMR spectroscopy, including homonuclear proton decoupling experiments as well as the H- and F-coupled ^{13}C NMR spectra. In all 1*H*-1,3-diazepines where a choice exists, the NH proton is observed only in the sterically least hindered position; this includes also compounds **17a** and **19a** mentioned below. The isomeric 7- and 6-trifluoromethylpyridines **12** and **15** give rise to 1 : 2 mixtures of the 1*H*-1,3-diazepines **13a,c** and **14a,c** in overall yields of 70–72%. These compounds were identified by their ^1H and ^{13}C NMR spectra. Benzoylation again gave 1-benzoyl derivatives **13b,d** and **14b,d** (Scheme 3).

The bis(trifluoromethyl)tetrazolopyridine **16** afforded the 1*H*-1,3-diazepines **17a,c** in 93–95% yield after room temperature photolysis for 90 min.‡ The *N*-benzoyl derivative **17c** was prepared as above.

Chlorotrifluoromethyl-substituted 1*H*-1,3-diazepines **19a–c** are obtained analogously, albeit in somewhat inferior yields (Scheme 3).

6,8-Dichlorotetrazolo[1,5-*a*]pyridine **20** was prepared from 2,3,5-trichloropyridine with hydrazine hydrate (95% yield of 2-hydrazino-3,5-dichloropyridine; mp 179 °C) followed by diazotization (87% yield of **20**; mp 78–79 °C; also obtainable by direct azidation of the trichloropyridine with NaN_3 in DMF). Photolysis of **20** in the appropriate amine gave **21a** and **b** in *ca.* 46% yield whereby one of the ring chlorines has been substituted for the dialkylamino group. The dichloropyridine **20**



Scheme 1 *Reagents and conditions*: i, *hν*, dioxane–methanol (3 : 1), 25 °C, 80 min, 92%; ii, as in (i), 47%, *ca.* 5% of 2-amino-3-trifluoromethylpyridine also formed (GC–MS); iii, BuLi, THF, −80 °C; iv, PhCOCl, −80 °C, 87%; v, H_2/Pd, MeOH, 25 °C, 14 h, 87%.

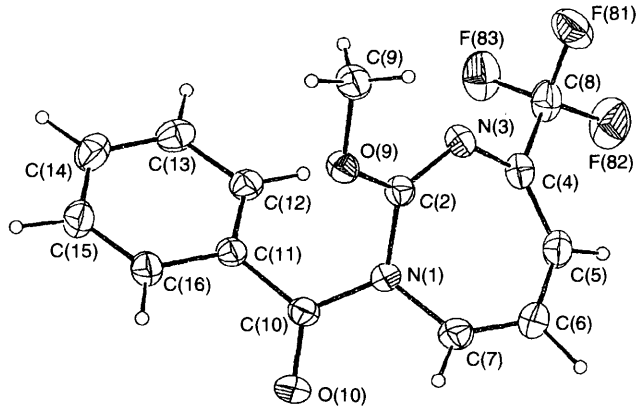
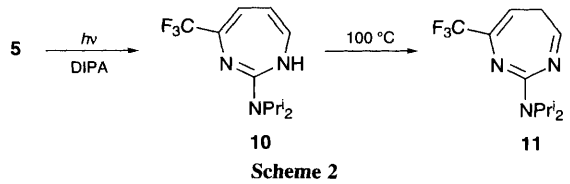


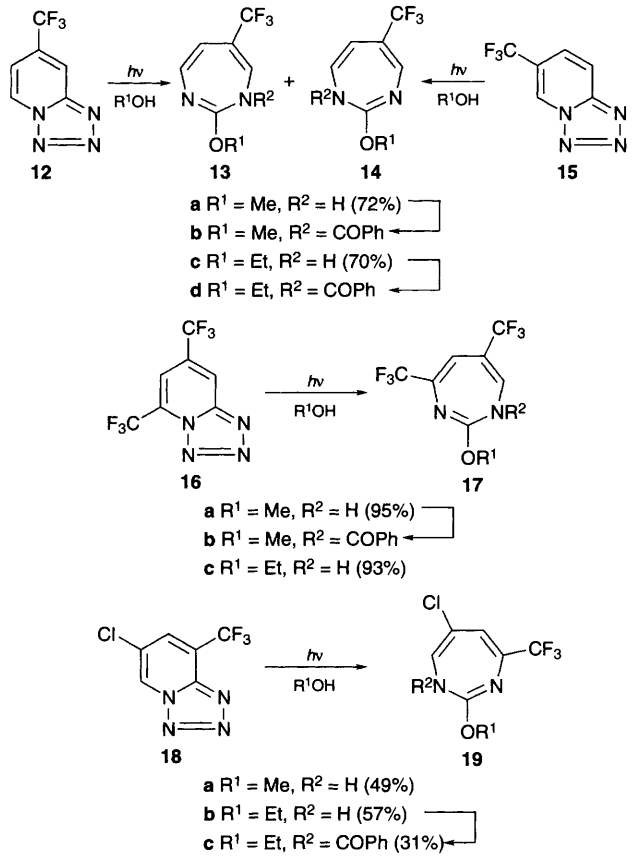
Fig. 1 ORTEP drawing of **8** (20% probability level)



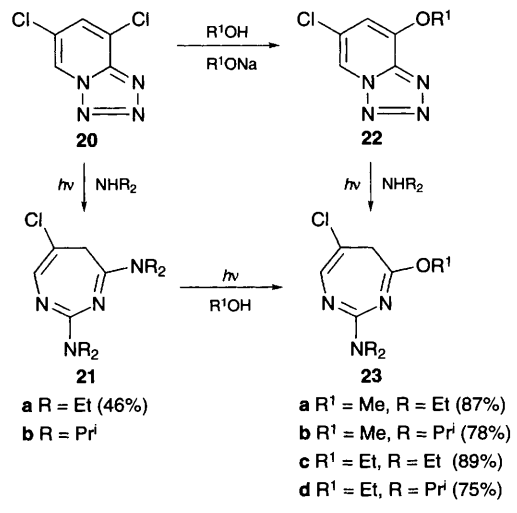
Scheme 2

undergoes an exchange reaction with sodium alkoxide in alcohol in the dark at room temperature (3 days) to provide the alkoxychlorotetrazolopyridines **22** in quantitative yields. Photolysis of the latter in the presence of amines gives exclusively 5*H*-1,3-diazepines **23a–d**‡ in good yields (Scheme 4).

Investigation of the factors influencing the stabilities and tautomerisation of 1*H*-, 5*H*-, *etc.* 1,3-diazepines is in progress and will be reported in due course.



Scheme 3



Scheme 4

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Footnotes

† All photolyses were carried out using a 1000 W high pressure Hg lamp and quartz vessels. Solutions were purged with N_2. Products were purified by column chromatography on silica gel 100 and/or Kugelrohr distillation at 100 °C, 0.01 millibar (1 bar = 10^5 Pa).

‡ All new compounds gave satisfactory analytical (C, H, N) and/or HRMS data. ^{1}H and ^{13}C NMR data are available for all compounds; *J* values are given in Hz. *Selected data* for **7** ^{1}H NMR ($CDCl_3$) δ 3.73 (s, OMe), 4.80 (br, 1 H, NH), 4.94 (dd, 1 H, 6-H, $J_{5,6}$ 5.4, $J_{6,7}$ 7.8), 5.45 (dd, 1 H, 7-H, $J_{6,7}$ 7.8, $J_{1,7}$ 5.1) and 5.84 (d, 1 H, 5-H, $J_{5,6}$ 5.4); ^{13}C NMR ($CDCl_3$) δ 56.1 (OMe), 110 (d, 6-C), 117 (d, 5-C), 121 (CF_3), 133 (d, 7-C), 138 (4-C) and 158 (2-C); ν/cm^{-1} 1688s. For **8** ^{1}H NMR ($CDCl_3$) δ 3.52 (s, OMe) 5.98 (dd, 1 H, 6-H, $J_{5,6}$ 5.7, $J_{6,7}$ 7.1), 6.48 (dq, 1 H, 5-H, $J_{5,6}$ 5.7, $J_{5,CF3}$ 1.1), 6.54 (dd, 1 H, 7-H, $J_{6,7}$ 7.1, $J_{5,7}$ 0.4) and 7.40–7.62 (m, 5 H, Ar-H); ^{13}C NMR ($CDCl_3$) δ 57 (OMe), 116 (5-C), 119 (6-C), 121 (CF_3), 129 (7-C), 138 (4-C), 149 (2-C), 167 (C=O), 127, 129, 132 and 134 (phenyl); ν/cm^{-1} 1691 (C=O) and 1648 (C=N); X-ray structure: see below. For **9** ^{1}H NMR ($CDCl_3$) δ 1.8–2.0 (m, 2 H, 6-H), 1.55–2.15 (m, 2 H, 5-H), 2.95 and 4.55 (m, 2 H, 7-H), 3.31 (OMe), 3.95 (m, 1 H, 4-H, $^3J_{CF3}$ 7) and 7.4 (m, 5 H, Ar-H); ^{13}C NMR δ 23.8 (5-C), 25.8 (6-C), 42.9 (7-C), 55 (OMe), 60.0 (4-C), 125.5 (CF_3), 156.3 (2-C), 169.2 (C=O), 127, 128, 131 and 136 (phenyl); ν/cm^{-1} 1692 (C=O) and 1659 (C=N). For **17a** ^{1}H NMR ($CDCl_3$) δ 3.76 (OCH_3), 5.1 (br, 1 H, NH), 5.79 (s, 1 H, 5-H) and 6.04 (d, 1 H, 7-H, $J_{1,7}$ 7.25); ^{13}C NMR ($CDCl_3$) δ 57 (OCH_3), 112.6 (5-C), 112.8 (6-C), 120.6 (6-CF_3), 122.8 (4-CF_3), 136.5 (7-C), 139.5 (4-C) and 157.3 (2-C). For **23a** ^{1}H NMR δ 1.08 (t, 6 H, CH_3), 2.99 (s, 2 H, 5-H), 3.37 (q, 4 H, CH_2), 3.73 (OMe) and 6.69 (s, 1 H, 7-H); ^{13}C NMR ($CDCl_3$) δ 13 (2 CH_3), 39.5 (5-C), 42 (2 CH_2), 55 (OMe), 103 (6-C), 136 (7-C), 154 (4-C) and 159 (2-C).

Crystal data for **8**: $C_{13}H_{11}F_3N_2O_2$, *M* = 296.25, monoclinic, space group $P2_1/n$, *a* = 10.742(2), *b* = 11.2020(10), *c* = 11.830(4) Å, α = 90°, β = 104.434(9)°, γ = 90°, *U* = 1378.6(5) Å^3, *F*(000) = 608 electrons, *Z* = 4, D_c = 1.427 g cm^{-1}, μ (Mo-Kα) = 0.124 mm^{-1}, Mo-Kα radiation (λ = 0.71073 Å). Crystal size 0.10 × 0.10 × 0.10 mm, *T* = 298(2) K. Data were collected on an Enraf-Nonius CAD4 four-circle diffractometer by theta scan type, within the limits 2.29 < θ < 24.97°. 2414 unique reflections were collected (R_{int} = 0.0180); 1339 refl. with $I > 2\sigma(I)$, R_1 = 0.0437, wR_2 = 0.1401, *s* = 0.784. Structure solved by direct methods (SHELXS 86) and refined (F^2) (SHELXL 93). Hydrogens were located by difference methods and refined isotropically. All other atoms were refined anisotropically. Atomic coordinates, bond lengths and angles, and thermal parameters have been deposited at the Cambridge Crystallographic Data Centre. See Notice to Authors, Issue No. 1. Any request to the CCDC for this material should quote the full literature citation and the reference number 182/1.

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